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Review

MAPK and β-Catenin signaling: implication and interplay in orthodontic tooth movement

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Abstract

Orthodontic tooth movement (OTM) requires the orthodontic forces (compressive and tensile strain) to subject to the periodontal ligament and mechanosensory cells in the periodontium and to achieve mechanotransduction by mechanoreceptors. In the context of OTM, a diverse array of signaling pathways are activated in mechanosensory cells that modulate bone resorption and formation in *in vitro* and *in vivo* models. The underlying molecular signal transduction, such as MAPK and β-Catenin signaling, that is involved in OTM, has been partially identified. It includes, but is not limited to genes and proteins which are related to osteogenesis, osteoclastogenesis, cementogenesis and inflammation. However, the interactive relation of β-Catenin and MAPK signaling remains ambiguous and diverse cross-talks are acting with each other. In this comprehensive text, we review the biology of OTM and reported experimental results on the activation/inhibition of these two signaling pathways during OTM. Here, we also focus on the implications and interplays between the MAPK and β-Catenin signaling in mechanosensory cells in response to orthodontic forces. Finally, the potential of further investigation strategies aimed at supporting orthodontic interventions are discussed. This review provides a conceptual framework for more comprehensive knowledge about signaling interaction during OTM.

Keywords: Orthodontic tooth movement; Orthodontic force; Mechanosensory cells; MAPK; β-Catenin; Mechanotransduction; Mechanoreceptors; Osteogenesis

1. Introduction

The conventional mitogen-activated protein kinase (MAPK) signaling is known as one of the fundamental pathways in cellular response during orthodontic tooth movement (OTM), and its activation regulates periodontal cell homeostasis [1] and innate immune responses [2]. This pathway is not only of vital importance in bone/cementum mineralization, but also for modulation of the periodontal ligament in response to orthodontic force [3].

The Wnt-sensitive signaling pathway is separated into the canonical signaling pathway which depends on the function of β-Catenin (termed Wnt/β-Catenin pathway) and the non-canonical pathway [4]. The former includes critical molecular cascades for cellular metabolism [5] and is essential for bone/cementum remodeling in response to orthodontic force [6]. A critical review by Duan *et al.* [7] claims that β-Catenin clearly plays roles not only in normal bone and tooth formation and development but also in mechanosensation and transduction in mechanosensory cells.

In general, OTM is composed of three stages on the compression side: a gradual compression of the periodontal ligament (PDL) (last from about 4–7 days), the hyalinization period (last from 7–14 days or more) and the direct bone resorption [8]. On the tension side, the PDL is firstly stretched and blood flow is activated, stimulating osteoblastic activity and mineralization [8].

However, the details of the molecular regulation of mechano-dependent cross-talks between MAPK and β-Catenin during OTM are not fully understood. Therefore, the functions of the β-Catenin and MAPK signaling pathway under orthodontic force will be the subject of this review based on cell- and animal-research. It will also cover the interaction roles how these two pathways relate to each other and their functions in the formation and maintenance of bone/cementum.

2. The biology in orthodontic tooth movement

The aim of orthodontic therapy is to align malpositioned teeth to an optimal functional position through the remodeling of the periodontium by application of mechanical force (termed orthodontic force) [9]. Orthodontic force causes tissue remodeling of the periodontium on the compression side (bone resorption) and on the tension side (bone formation). Also unexpected, orthodontically induced inflammatory root resorption (OIIRR) may occur if unsuitable forces are applied. Thus, OTM is induced by external orthodontic force and is promoted by the controlled processes of alveolar bone/cementum remodeling. Clinically, the forces are usually achieved by direct bonding of orthodontic brackets [10]. The orthodontic treatment with brackets might cause changes in the oral microbiota, leading to an increased number of microorganisms not only in

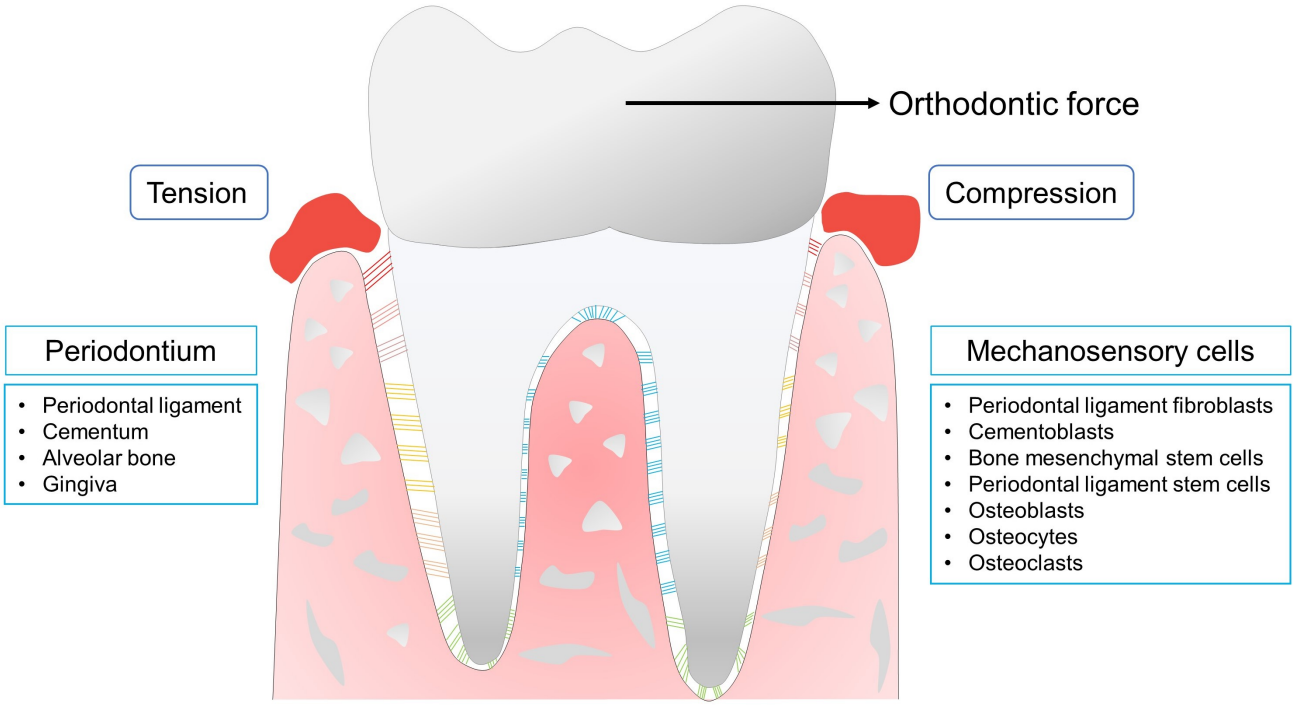

Fig. 1. Components of the periodontium and mechanosensory cells in OTM.

saliva, but also in the dental plaque [11]. Orthodontic brackets may impede a proper oral hygiene, thus contributing to the initiation of an inflammatory process by plaque accumulation and favoring gingivitis, gingival enlargement, increase in pocket probing depth, bleeding on probing [11] and white-spot lesion on enamel [12].

At the cellular level, PDL fibroblasts maintain the normal width of the PDL by preventing the encroachment of bone and cementum into the PDL space and are the first responsible cells in response to orthodontic force. OTM requires the coordinated action of mechanosensory cells which include PDL fibroblasts [13], cementoblasts, bone mesenchymal stem cells (BMSCs), periodontal ligament stem cells (PDLSCs), osteoblasts, osteocytes, and osteoclasts [14] to regulate alveolar bone/cementum remodeling by converting orthodontic force into intracellular signals [15–17]. Among these cells (Fig. 1), PDL fibroblasts are the first recipients of mechanical forces during OTM [18] with the capacity to integrate orthodontic force and mediate the bone remodeling process [19]. Orthodontic forces applied to teeth initially induces the fluid movement in the PDL space and distortion of the PDL component, causing the release of numerus of molecules which initiate the bone/cementum remodeling [20]. Also, PDLSCs play important roles in periodontal homeostasis during OTM [15,21]. PDLSCs share characteristics with BMSCs [22] and have the potential to differentiate into cementoblasts or osteoblasts [23].

To investigate the inter- and intra-cellular signaling pathways, researchers have established several *in vitro* models to mimick the two major orthodontic forces, tension and compression, that occur during OTM [24–26]. There are two main methods to apply forces. Tension is achieved via substrate deformation [27], whereas compression is mainly applied via weight [28,29], hydrostatic pressure [30], or centrifugation [24,31].

Unfortunately, it is still unclear how these mechanosensory cells exactly recognize the orthodontic force and convert it into cellular signals. Different mechanosensors/mechanoreceptors have been proposed, including the cytoskeleton, membrane Ca^{2+} permeable channels [32], primary cilia, focal adhesions, and gap junctions [33]. Focal adhesions which sited with integrin receptors attach the PDL fibroblasts to each other [34]. Therefore, integrins transmit forces across the cell membrane, and integrin receptors are candidates of mechanoreceptors [35]. The stimulation of appropriate orthodontic force leads to periodontal tissue reconstruction by adaptive changes at the molecular level in different microenvironments, including the extracellular matrix, cell membrane, cytoskeleton, nucleoprotein and genome [36]. As a consequence, intracellular signals are activated upon extracellular force stimuli and transduced to the cell nucleus, regulating the expression of genes. Multiple signaling pathways mediate the response of mechanosensory cells to orthodontic force, including the β-Catenin and MAPK pathway that are both involved in this biological process, triggering a series of biological reactions [37]. Furthermore, recent advances suggest a possible intersectional cross-reacting network. The

β-Catenin signaling in-turn is mediated by the MAPK signaling pathway [38,39]. The functions of the MAPK and β-Catenin pathways in OTM are discussed in more detail below.

3. MAPK signaling and its activation in OTM

3.1 MAPK signaling

The MAPK pathway is mainly composed of three subfamily members, including extracellular signal-regulated kinase (ERK)1/2, ERK5, c-Jun N-terminal kinase (JNK1/2/3) and P38 mitogen-activated protein kinase (P38$\alpha/\beta/\gamma/\delta$ MAPK), which after cascade phosphorylation, are transmitted to the nucleus and regulate the expression of downstream transcription factors [40]. The MAPK pathway operates in a three-tiered cascade: MAP kinase kinase kinases (MAP3K), MAP kinase kinases (MAP2K), and MAPKs [41]. MAPKs are widely expressed in various forces-stimulated mechanosensory cells to regulate transcription, and therefore influence bone/cementum homeostasis [42]. In detail, once the orthodontic forces reach the mechanosensory cells and activate mechanosensors, MAP3K (RAF) are induced and phosphorylate the downstream MAPK kinases MAP2K (MEK/MKK), which in-turn phosphorylate and activate MAPKs [43]. Through such cascade reactions during OTM, MAPKs are implicated in extracellular orthodontic forces, transduce extracellular signals into different cellular actions and regulate gene/protein expressions which are closely associated with bone resorption of osteoclasts and bone formation of osteoblasts [36]. Of the three classic MAPKs, scientific evidence predominantly points to ERK1/2 and P38 as being involved in osteogenesis-associated gene expression and bone formation *in vivo* [44,45].

3.2 Activation of MAPK signaling in OTM

Orthodontic force-induced phenotypic change of the PDL can involve the activation of MAPK signaling pathways [46]. For instance, orthodontic forces trigger the MAP3K/MAPK2K/ERK kinase cascade through facilitating RAF/RAF, RAF/MEK, and MEK/MEK interactions as well as subsequent phosphorylation [47]. Thus, ERK1/2 are activated and accumulate in the cytoplasm, where they phosphorylate a series of substrates that regulate PDL homeostasis [47]. The ERK1/2 pathway, a main channel through which extracellular matrix formation is induced, participates in a variety of cellular biological responses and bone signal reactions in PDL. Besides, hyperactive MAPK signaling also initiates negative feedback loops, which correct cells back to quiescent status [48].

On the tension side, orthodontic force promotes that the progenitor cells in the PDL proliferate and differentiate into osteoblasts [49]. The tensile forces have been shown to activate ERK1/2 in osteoblastic cells *in vitro* followed by new alveolar bone formation [46]. Cyclical tension stress of 10% at 0.5 Hz enhanced osteogenic differentiation of human PDLSCs through activation of the ERK1/2 MAPK signaling pathway [50]. Furthermore, ERK1/2 increases the expression of alkaline phosphatase (AP) and enhances matrix mineralization [51]. In detail, the activated ERK1/2 signal participates further into different cellular responses such as collagen synthesis [52], cyclo-oxygenase expression [53] and osteopontin production [54] in OTM. Nakashima *et al*. (2002) have also shown that orthodontic force could promote runt-related transcription factor 2 (Runx2) expression, which promotes many osteoblast-specific genes such as osteocalcin (OCN), collagen type I (Col I), bone sialoprotein (BSP), osteopontin, AP, and collagenase-3 through the ERK1/2 pathway *in vitro* [55]. Consistent with their findings, Kawarizadeh *et al*. [19] reported that a short-term orthodontic force promoted the expression of Runx2 which was achieved via the ERK1/2 pathway in their rat model. However, Karasawa *et al*. [56] showed that tension force decreases the phosphorylated ERK1/2 but increased the expression of phosphorylated JNK in osteoblasts.

On the compression side, evidence suggests that in different mechanosensory cell types MAPK signaling is involved and through this AP activation [57–61]. When 2.4 gf/cm^2 compressive force was applied to cementoblasts, the P38 MAPK kinase was immediately activated and ERK1/2 MAPK and JNK signalings were activated 0.5 h after the exposure [62]. At the same time, the inhibition of JNK and P38 reduced the compression-associated proliferation and AP expression of cementoblasts [62]. In contrast, Perinetti *et al*. [63] showed that AP activity is decreased in human dental pulp tissue in the early-phase of OTM. Tsutsumi *et al*. [32] reported that intermittent compressive force activates the ERK1/2 and P38 MAPK pathway in human PDLSCs. Diercke *et al*. [18,64] showed that 30.3 gf/cm^2 of static compressive forces induced the phosphorylation of ERK1/2 expression in human PDL fibroblasts. ERK2 was reported to be a key regulatory molecule in three-dimensionally (3D) cultured human PDL cells after application of compressive stress for 48 h [65]. Pavlidis *et al*. [66] verified that constant forces for 4 h of 0.25 and 0.5 Newtons (N) applied in witstar rats, upregulated the expression of phosphorylated-ERK1/2 on PDL cells. In addition, Jiang *et al*. [36] demonstrated that orthodontic tension stress of 40 newtons in rat and human PDLSCs exposed to centrifugal force of 80 $\times$ grams, resulted in a time-dependent alteration of phosphorylation of ERK1/2 and P38 protein and mRNA expression consistently. Under orthodontic strain of 10% and elongation at 1 Hz, activation of the ERK 1/2-Runx2 intracellular pathway in BMSCs results in their differentiation into bone forming osteoblasts [67]. In response to orthodontic forces (magnitude: 0.1, 1, 6 MPa; time: 10, 30, 60 min; frequency: 1 Hz), the P38 MAPK signaling has the ability to increase the production of inflammatory cytokines and RANKL in osteoblasts, thus initiating osteoclastogenesis and promoting bone remodeling [68]. This indicates that the selective

activation of the MAPK intracellular signaling pathway is determined by the magnitude of the applied force [69].

The activation of ERK1/2 and P38 signaling pathways induced by orthodontic force are associated with the up-regulation of AP, OPN, Col I, OCN and BSP in mRNA expression levels in human PDLSCs [36]. It was suggested, that these five genes may be influenced by other signaling pathways, including bone morphogenetic protein (BMP) and Wnt/β-Catenin [70,71].

4. β-Catenin signaling and its roles in OTM biology

4.1 β-Catenin signaling and cellular homeostasis

In this section, the widely studied pathway referred to as the canonical Wnt/β-Catenin signaling pathway will be addressed. This molecular pathway has recently been implicated as an important inducer of bone/cementum formation [5]. The protein β-Catenin is the central target and an essential component of the Wnt/β-Catenin signaling pathway [72].

Under regular homeostasis, cellular β-Catenin is degraded by the "degradation complex" proteosome consisting of adenomatous polyposis coli (APC) protein, glycogen synthase kinase-3β (GSK-3β) and axin. This complex facilitates the phosphorylation of β-Catenin by the GSK-3β at the Serine-9 (Ser9) residue that ultimately causes ubiquitylation and proteasome-mediated degradation of β-Catenin [73].

However, upon stimulatory activation (i.e., Wnt ligands) by binding to the receptors of the seven-pass transmembrane receptor frizzled (FZD) and the coreceptors of the low-density lipoprotein receptor-related proteins (LRPs) -4, -5 or -6 at the cell membrane [74], phosphorylated LRPs are induced in the cytoplasm. This in turn recruits axin from the "degradation complex" to bind to this phosphorylated site. Then the complex is dissociated by cytoplasmic protein disheveled (DVL) to release β-Catenin. Afterwards, β-Catenin starts to be freed from the degradation complex. Thus, there is an accumulation of cytoplasmic β-Catenin leading ultimately to its translocation into the nucleus where it exerts stimulatory effects on lymphoid-enhancer factor/T-cell (TCF/LEF) factor, leading to the activation of developmentally related genes [75,76]. These target genes mediate osteoblastogenesis which in consequence induces bone formation, thus these genes are important in the cellular responses to orthodontic force [77]. In the absence of Wnt signal, the free intracellular levels of β-Catenin are kept low [78].

The β-Catenin signaling pathway was found to cross-talk with BMP2 signaling and other factor signaling pathways to regulate osteoblastic anabolic function in bone [79], which also increases the difficulty of studying and understanding this pathway [80]. However, β-Catenin is one component which remains a single constant target of this pathway [81]. It's well known that β-Catenin is a crucial regulator for canonical Wnt/β-Catenin pathway activation, which is essential for proper bone development and down-regulation of this pathway impairs bone formation [82,83]. What's more, β-Catenin is involved in cementogenesis by the cementum protein (CEMP) and cementum attachment protein (CAP) expression in human PDLSCs [84]. GSK-3β plays more important roles in bone remodeling compared to GSK-3α. Both include two types of isoforms of the key regulator of glycogen metabolism GSK-3.

4.2 Activation of β-Catenin signaling in OTM

Data from murine models suggest that the β-Catenin signal participates in bone remodeling and is critical for bone homeostasis during OTM [15,85]. It was revealed, that the "degradation complex" containing GSK-3β constitutively phosphorylates the N-terminus of β-Catenin at Ser45 and thus enables the ubiquitination of β-Catenin, which finally marks β-Catenin for degradation. This state is reversed when GSK-3β is phosphorylated at Ser9, that blocks its ability to phosphorylate β-Catenin [86]. Consistent with that mechanism, orthodontic force applied in mice models elevated phosphorylated-GSK-3β (Ser9) expression and β-Catenin signaling pathway activation could increase the bone formation during OTM [86,87]. Orthodontic forces decreased GSK-3β levels and the latter further increased bone mineral density, trabecular thickness as well as AP-positive cells at tension sites during OTM, indicating GSK-3β is negatively related to the deposition of new bone at the tension site in OTM [87].

On the compression side during OTM, Wnt10b ligand and β-Catenin mRNA expression were inhibited in the initial stage and thereafter increased on the pressure side, reaching a peak at day 5 in a rat model [1,88]. Subsequently, the accumulation of β-Catenin signaling regulated the expression of osteogenesis- and osteoclastogenesis-related genes in response to orthodontic forces [89,90]. Premaraj *et al*. [86] showed that compressive force induced increasing phosphorylation of GSK-3β which induced the intensive β-Catenin nuclear translocation, demonstrating inactivation of GSK-3β by 2.2 gf/cm^2 compressive force. Moreover, mice engineered with a loss-of-function mutation in the LRP5 gene express reduced bone mineral density and reduced osteogenic response to orthodontic forces [91]. Mice with global gain-of-function LRP5 gene show significantly increased bone mass and bone mineral density in response to orthodontic force [92,93]. During OTM, gain-of-function mutations of LRP5 decreased the rate of OTM as a result of the increased alveolar bone mass and the reduced osteoclast-mediated bone resorption [94]. In another rat OTM model, Wnt3a and Wnt10b, two major ligands of Wnt/β-Catenin signaling pathway, as well as β-Catenin levels, are much stronger expressed on the tension side what is consistent with Wnt ligands-induced bone formation observed under tension. The Dkk-1 level, a Wnt inhibitor, is much higher expressed on the compression side

that comes along with reduced Wnt ligands and greater bone resorption on the compression side [95].

Supporting evidence shows β-Catenin is also expressed in primary human PDL cells [86], in osteocytes [96] and cementoblasts [62] under orthodontic force. The compressive force activated the β-Catenin signaling components functionally and β-Catenin serves as an effector of mechanical signals in PDL cells [86]. On the tension side, it was reported, that cyclic tensile stress of 20% elongation to cultured human PDL cells decreased the expression of the phosphorylated GSK-3β and β-Catenin proteins, suppressing the canonical Wnt/β-Catenin signaling pathway in PDL cells [97].

In response to orthodontic force, the β-Catenin increases [98], suggesting that β-Catenin regulated mechanotransduction in the PDL [99]. Thus, the canonical β-Catenin signaling pathway upregulated the expression of genes which are able to induce the osteoblastogenesis and cementogenesis and increase the ratio of OPG/RANKL, followed by inhibited osteoclastogenesis [6,100]. With the transcriptional activation of numerous osteogenic/cementogenesis genes, β-Catenin promotes the differentiation and maturation of osteoblasts to form bone during OTM [6]. Furthermore, the applied orthodontic force stimulates the mechanosensory cells in the PDL and alveolar bone to release proinflammatory, angiogenic, and osteogenic substances [101]. In combination with the activated β-Catenin, the remodeling process of the PDL and adjacent alveolar bone is activated, finally enabling tooth movement [101,102].

Similar to alveolar bone formation, β-Catenin signaling plays a critical role in cementum formation [103,104]. For instance, ablation of β-Catenin in a rat model leads to decrease of BSP in mRNA levels, a marker for cementogenesis. In contrast, activation of β-Catenin leads to excessive cementum formation [103,104]. *In vitro*, Wnt3a promotes the differentiation of human BMSCs into cementoblast-like cells [105,106]. It is probable, that the Wnt/β-Catenin signaling pathway interacts with other intracellular signaling pathways such as MAPK and these interactions regulate bone/cementum remodeling [6,98].

5. The cross-talk between MAPK and β-Catenin signaling

A multitude of highly insightful studies have implicated the possible cooperative interaction between the Wnt/β-Catenin and MAPK signaling pathways (Fig. 2) [38,39,107,108]. The Wnt/β-Catenin interacts with P38 MAPK at different levels [43]. For example, Bikkavilli *et al*. [38] reported that the activation of P38 MAPK regulates canonical Wnt/β-Catenin signaling via inactivation of GSK-3β kinase activity. Meanwhile, P38 is able to enhance the Wnt/β-Catenin signaling. For instance, down-regulation of the β-Catenin signaling is mediated by P38 MAPK during cartilage development in chick wing bud mesenchymal cells [109]. On human dental pulp cells, the elevation of β-Catenin resulting from BMP2 stimulation is mediated by the P38 MAPK pathway, as the P38 inhibitor prevented these effects [110]. Indeed, the blockade of the P38 MAPK signaling affects the triggering of the Wnt3a downstream event [111–113]. Ehyai *et al*. [112] reported that P38 MAPK signaling reinforced the β-Catenin accumulation via P38-mediated phosphorylation of myocyte enhancer factor 2 (MEF2) in Wnt3a-stimulated primary vascular smooth muscle cells. For other cell types, it was described that inhibition of dual phosphorylated ERK1/2 leads to increased β-Catenin signaling on melanoma cells [113]. On the contrary, inhibition of JNK as well as inhibition of P38 attenuates Wnt3a-induced β-Catenin up-regulation via GSK-3β inactivation by phosphorylating its Ser9 on mouse totipotent embryonal F9 cells [111] and on mouse embryonic carcinoma cells [38]. Bikkavilli *et al*. [111] also concluded that JNK activation by Wnt3a occur LRP5 independently and suggested that Dishevelled 2 receptor but not Dishevelled 1 or 3 are committed in cell activation. Caverzasio *et al*. [114] reported that inhibition of β-Catenin transcriptional activity by the P38 inhibition is independent of LRP5/6 [115]. In addition, Wnt/β-Catenin signaling is required for ERK1/2 activation in calvarial osteoblasts [116]. ERK1/2 signaling could in-turn stabilize β-Catenin by phosphorylation of GSK-3β [117].

In the regulation of bone remodeling, the activation of β-Catenin was reported to protect the osteoblast and osteocyte from apoptosis via ERK1/2 signaling [118]. In addition, ERK1/2 is able to activate the canonical Wnt/β-Catenin signaling [119], indicating a feed-forward loop that amplifies the anti-apoptotics effect of the ERK1/2 signaling pathway through Wnt/β-Catenin signaling. Also, Gortazar *et al*. [120] demonstrated in a tension force model that ERK1/2 activation is required for β-Catenin accumulation induced by mechanical stimulation in mechanotransduction, leading to osteocyte survival. Thus, the orthodontic force induced ERK1/2 and stabilized β-Catenin in an interdependent fashion. Moreover, MAP3K, an upstream activator of the MAPK pathway, mediated phosphorylation of β-catenin working as stabilizer of β-catenin as an alternative pathway in osteoblasts (Fig. 2) [121].

Corresponding with these findings, our recent studies lead to a novel finding detected in the cementoblasts under compressive force [98]. It was demonstrated that JNK, ERK1/2 as well as P38 chemical inhibition reduces the β-Catenin expression on cementoblasts. JNK1 and P38α silencing negatively regulated β-Catenin, whereas ERK1 had a significant positive effect on the GSK-3β expression. Furthermore, the β-Catenin expression was up-regulated after compression was applied. This reciprocal interaction points towards a negative feedback loop between MAPK and β-Catenin during OTM.

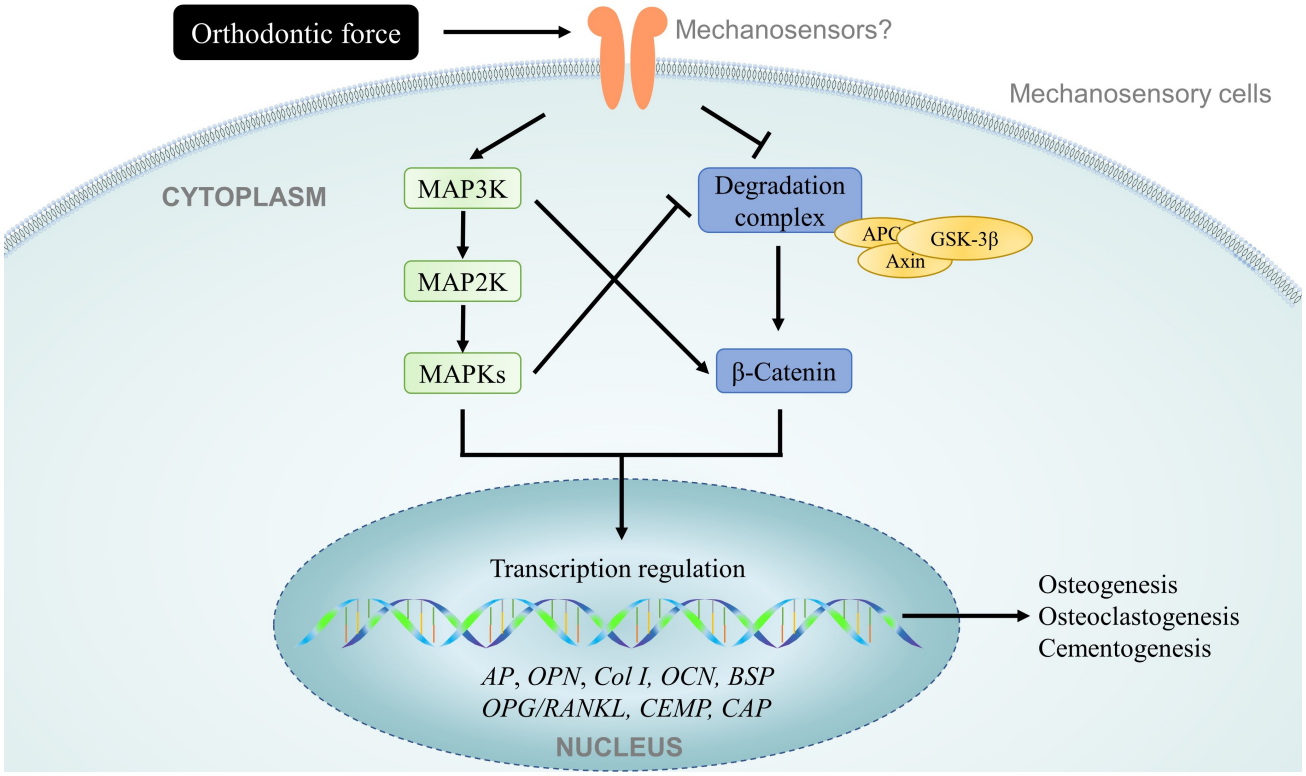

Fig. 2. The schematic diagram illustrates the proposed molecular interactions between MAPK signaling pathways and β-Catenin on mechanosensory cells cultivated under orthodontic forces. Activation of MAPKs, specially P38 MAPK and ERK1/2, promote the accumulation of β-Catenin signaling via inactivation of GSK-3β kinase activity. MAP3K promote the stabilization of β-Catenin as an alternative pathway. A variety of molecules is involved in regulating the homeostasis of mechanosensory cells after application of orthodontic force, including alkaline phosphatase (AP), osteopontin (OPN), collagen type I (Col I), osteocalcin (OCN), bone sialoprotein (BSP), osteoprotegerin (OPG)/RANKL, cementum protein (CEMP) and cementum attachment protein (CAP), which have been shown to modulate osteogenesis, osteoclastogenesis as well as cementogenesis.

6. Conclusions and future work

Here, we reviewed how the MAPK, β-Catenin signaling and their cross-talks with each other create signaling networks that play different roles for mechanosensory cells during OTM. To adapt to the particular circumstances that are induced by orthodontic forces, the MAPK pathway and β-Catenin pathway must be integrated into the overall signaling activities of the mechanosensory cells. The magnitude and duration of an orthodontic force will influence the biological response and thus needs to be controlled in the progress of OTM. The use of standardized orthodontic forces are helpful in aimed activation and interaction of these two signaling pathways to avoid the OIIRR.

Nonetheless, the precise molecular basis about how these two signaling pathways interact with each other and their impacts on OTM and OIIRR remains largely unresolved. For instance, it is unclear, how the various isoforms (i.e., ERK1/2, P38, JNK) of MAPK signaling differentially regulate the GSK-3β and β-Catenin and how this distinctly alters OIIRR. Besides, it has not been revealed yet, if the MAPK pathway is involved in the interaction with β-Catenin in other mechanosensory cells such as BMSCs during OTM. Addressing these questions would deepen our understanding of MAPK/β-Catenin interplay in OTM. Moreover, mechanoreceptors have important effects on the mechanotransduction of the orthodontic forces applied to these mechanosensory cells and need to be identified and the possible mechanotransductive signaling pathways are warranted for further investigation. It would be of interest to conduct transgenic experiments in *in vivo* models with constitutive activation or targeted deletion of MAPK or β-Catenin in mechanosensory cells, aiming to further investigate the interaction of MAPK/β-Catenin during tooth movement and OIIRR. Therefore, the role of MAPK/β-Catenin in alveolar bone and teeth will be a useful target for future investigations.

Abbreviations

OTM, orthodontic tooth movement; MAPK, mitogen-activated protein kinases; OIIRR, orthodontically induced inflammatory root resorption; PDL, periodontal ligament; BMSCs, bone mesenchymal stem cells; PDLSCs, peri-

odontal ligament stem cells; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; P38 MAPK, P38 mitogen-activated protein kinase; N, newtons; APC, adenomatous polyposis coli protein; GSK-3β, glycogen synthase kinase-3β; LRPs, lipoprotein receptor-related proteins; TCF/LEF, lymphoid-enhancer factor/T-cell; MEF2, myocyte enhancer factor 2; AP, alkaline phosphatase; OPN, osteopontin; Col I, collagen type I; OCN, osteocalcin; BSP, bone sialoprotein; OPG, Osteoprotegerin; CEMP, cementum protein; CAP, cementum attachment protein.

Author contributions

JWY and SG wrote the manuscript and participated in its modification. JM and SR conceived, conceptualized and supervised the review. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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